REMARKS

Status of Claims

Claims 1-32 were pending in the application and are subject to restriction and/or election requirement.

In view of Applicant's election of Group 1, claims 1-25 and 27 are under examination and claims 26 and 28-32 are withdrawn.

However, for reasons set forth in greater detail below, Applicants submit that the claims as presently amended clearly avoid the prior art which was the basis for the determination of "lack of common technical feature" in the Lack of Unity of Invention determination in the WO application. The present claims involve (a) testing of a body fluid sample and not a tissue sample, (b) perform a diagnostic test rather than monitoring progression of gene regulation during the course of sepsis, and (c) are directed to a method that can be practiced on live mammals rather than requiring sacrificing of rat. Since all claims are now believed to be directed to the same patentable invention (distinguishing between SIRS and sepsis) and common technical feature (analysis of body fluid), and unity of invention having been established (these claims not being obvious over the prior art of record in the WO application), it is respectfully requested that all claims be rejoined.

Restriction Requirement

The Examiner requires Applicants to restrict the application to one of the following inventions:

I. Group 1, claims 1-25 and 27, drawn to methods for differentiating systemic inflammatory non-infections conditions and systemic inflammatory infections conditions.

II. Group 2, claims 26 and 28, drawn to methods for assay calibration, and screening of therapeutics.

III. Group 3, claim 29, drawn to method of analysis of gene activities modulated by particular gene.

IV. Group 4, claim 30, drawn to methods of gene analysis related to sepsis or SIRS by electronic processing.

V. Group 5, claim 31, drawn to software production methods.

VI. Group 6, claim 32, drawn to methos to provide experimental systems for modeling cellular signal transmitter pathways.

In response Applicants elect **Group 1**, claims 1-25 and 27 as amended, with traverse, for the reason that at least Groups 2-4, if not all groups, should be grouped with Group 1.

Traversal of Lack of Unity Requirement

Applicants note paragraph 2 of the Restriction Requirement wherein the Examiner characterizes the "common technical feature" as "the differential gene activity associated with sepsis." The Examiner takes the position that this is known in the prior art and taught by Chinnaiyan et al. (2001), thus, the main claim is not patentable, and there is no common technical patentable claim.

Applicants respectfully traverse.

Chinnaiyan teaches that differential gene activity in ***certain organs of the body*** can be indicative of sepsis. Chinnaiyan only teaches the study of differential gene expression in the context of sepsis at the multiorgan level. Chinnaiyan requires sacrificing of experimentally infected animal and use of **body tissue**, taken from the lung, liver, thymus, spleen, kidneys, and brain of rats, as samples from which RNA is isolated for quantification of gene activity.

The present invention, on the other hand, claims a method of using differential gene activity of a particular type of gene for ***early*** detection of SIRS or sepsis, wherein RNA is taken from biological **body fluid** sample such as blood, serum, urine, peritoneal fluid, seminal fluid, saliva, tissue fluid, cellular contents, or a mixture thereof. The present invention does not study the course of gene expression in the context of studying progression of sepsis at the multiorgan level, but is instead concerned with the rapid and precise diagnosis of sepsis in a mammal, preferably a human patient. This is an important distinction between the claimed invention and

the prior art, because the claimed method does not necessitate the removal of body ***tissue*** for analysis. Therefore, the patient in whom sepsis is suspected does not need to undergo an invasive procedure for tissue removal. Instead, a quick and painless sample of blood, urine, saliva, or other bodily fluid can be taken. According to the specification:

> **[0021]** In the field of neurology a large number of studies were carried out for identification of gene active markers by means of microarray technology [36]. The same applied for the research of molecular changes, which could be triggered by individual components of bacterial Gram negative pathogens (for example using stimulation experiments with lipopolysaccharides) [37]. Such research was a rule carried out by means of the cellular model system, for example human endothelial cell cultures [38], or in human leucocytic cell cultures [41], or also for example **by means of research of human tissue but however not blood** in [39 (Chinnaiyan)].
>
> **[0058]** The description of the invention with respect to blood represents only one exemplary embodiment of the invention. The biologic fluids could, in the sense of the invention, be **any body fluids of the human**.

Basically, Chinnaiyan harvest organs at various stages in development of sepsis and screen DNA using a 8064 element microchip, identifying which genes are "up regulated" and which genes are "down regulated", and analyze the patterns of gene regulation in an attempt to elucidate the mechanism of the pathogenesis of sepsis. Chinnaiyan have no teaching relevant to the present invention, which provides a tool for early diagnosis of sepsis by measuring levels of expression of genes in bodily fluids of a patient (a mammal).

More specifically, Chinnaiyan discuss that, in surgical and medical intensive care units, sepsis often leads to pulmonary, hepatic and renal failure, this triad commonly being referred to as "multiorgan failure syndrome." "Although this pattern of organ failure is well-known clinically, its pathogenesis is poorly understood." (Discussion) Chinnaiyan "examined the temporal sequence of sepsis-induced gene expression patterns in major organ systems including lung, liver, kidney, thymus, spleen, and brain" (Abstract) in an attempt to elucidate the mechanisms of sepsis.

Chinnaiyan also explain usefulness of DNA microarray for testing many different genes at the same time (paragraph bridging pages 1199 and 1200), and explain that they developed an

8064 glass slide element rat cDNA microarray including ~2000 known, named genes to analyze multiorgan/multisystem gene expression patterns (page 1200, first col., last para., and results, first para.). "We propose that the response to sepsis induces both distinct and shared gene expression programs in various organs... Our hypothesis is that microarray analysis of genes expressed in organs during sepsis may be predictive of outcome, especially in organs that are known to be compromised during sepsis. Such studies may provide important insight into multiorgan failure during sepsis. Although several studies have successfully used DNA microarrays to molecularly classify malignancies, this is the first gene-profiling study to address an important disease process at a multiorgan, multisystem level."

Thus, Chinnaiyan hypothesize that by identifying via microarray analysis which genes are expressed during course of development of sepsis, they may better understand the mechanisms of sepsis. There is no hint as to relevancy of levels of expression of genes.

Chinnaiyan do not suggest a prognostic test to be conducted with living patients. Rather, they teach post mortem analysis of organs harvested at various times post-op to attempt to reconstruct disease progress over time at a multi-organ, multi-system level. "Lung, liver, thymus, spleen, kidneys, and brain were harvested from CLP rats, sham-rats, and control untreated rats. Various time points (6, 12, 18, and 24 hours) after surgery were used in the CLP and sham animals. Organs from three rats from each condition were pooled, snap-frozen, and stored at -80°C." (Materials and Methods) Such teaching is hardly suggestive of or applicable to diagnostic and preventative methods of the present invention.

Under *Microarray Analysis* Chinnaiyan teach DNA microarray analysis of gene expression. This test is a screening test, for identification of genes, not for quantification of levels of expression. Note that the microchips include various control elements. None of the control elements were designed for calibration or measurement of levels of expression. Test were carried out on pooled rat organs. Fluorescent images of hybridized microarrays were obtained using a GenePix 4000A microarray scanner (www.axon.com; Axon Instruments, CA).

As reported in *Data Analysis,* fluorescent images of hybridized microarrays were analyzed and genes were select as significantly up- or down-regulated relative to the control sample. The data sets for each organ were individually queried for genes that were differentially expressed in the CLP organs as compared to control organs, i.e, ratios >2.0 for up-regulated, or

<0.5 for down-regulated. Thus, Chinnaiyan are merely interested in identifying which genes are turned on, i.e., exceed or fall be low a threshold, and not the level of gene expression.

"[W]hen organs from septic animals were compared to respective control organs, differential gene expression was observed" (Fig. 1). "Gene expression was monitored in six organs at various times points (6, 12, 18, and 24 hours) in the CLP rat model. Hierarchical clustering of the data identified distinct patterns of gene expression in the organs studied. Red and green colors in the matrix represent genes that are up- and down-regulated, respectively, relative to the untreated control organ." (Fig. 2) Again, patterns of identified genes, not levels of gene activation, are studied. The patterns of gene expression in each organ are compared.

The section *Validation of Selected Genes Identified by Microarray Analysis* discusses levels of expression, but only as part of validation check. There is no suggestion that expression levels have any relevancy to sepsis.

Finally, by identifying which genes are regulated, Chinnaiyan identify or at least postulate a pathway of sepsis. "Thus, our data suggest that several tissues mobilize downstream components of the IL-6 signaling pathway in response to sepsis and are presumably primed for activation by IL-6." (*Functional Analysis of Sepsis-Induced Gene Expression Patterns)*

Applicants respectfully refer the Examiner to the present claims which have been amended to emphasize the restriction to ***body fluid***.

In light of these important and significant distinctions between the claimed invention and the prior art, Applicants respectfully traverse the Examiner's rejection of the claimed invention's common technical feature as being not special in view of prior art. It is respectfully submitted that al claims recite a common unifying feature and should be considered together.

At a minimum, at least the invention according to **Groups 1-4** (claims 1 through 30) should be examined together. Examination in a single application would not be an undue burden on the Examiner as these claims can easily be searched and examined at the same time. The Examiner has provided no showing that it would be burdensome to examine these claims together.

Finally, Applicants submit, pursuant to MPEP § 803, that the invention of claims 1 through 30 would have been obvious over each other. If there is an express admission that the

claimed inventions would have been obvious over each other within the meaning of 35 U.S.C. § 103, restriction should not be required. *In re Lee*, 199 USPQ 108 (Comm'r Pat. 1978).

Accordingly, withdrawal of the restriction requirement is respectfully requested.

Further Lack of Unity Requirement

In view of election of Group 1, the Examiner requires Applicant to select a single specific combination of genes. In response, the Applicants select with traverse the combination of SEQ ID NOs 1-10, 78, 79, 81 and 87, the sequences being those listed in Table 2 of the present application and exhibiting the greatest elevation of expression:

SEQ ID NO	Accession No.	HUGO-Name
1	NM_006986.2	MAGED1
2	NM_005319.1	H1F2
3	NM_001925.1	DEFA4
4	NM_006516.1	SLC2A1
5	D87452.1	IHPK1
6	NM_020070.1	IGLL1
7	NM_022771.1	FLJ12085
9	NM_001738.1	CA1
10	L05148.1	ZAP70
78	BC017356.1	IGHM
79	AB007950.2	KIAA0481
81	X17263.1	IGKV1D-12
87	U65404.1	KLF1

Traversal is for the reason that, in the present invention, the sample RNA is isolated from body fluids such as blood, serum, urine, peritoneal fluid, seminal fluid, saliva, tissue fluid, cellular contents, or a mixture thereof, and not from organ tissue, as taught by the prior art, thus all species are within the same invention. All identified species can be used in the same manner as early indicators of sepsis or SIRS, in view of their over expression or under expression.

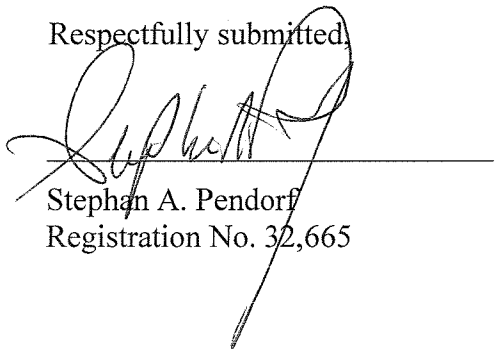
Applicants do not clearly understand the relationship between the "Restriction" (different inventions), "Election" (different species but same invention), and "Further Lack of Unity" (under which the Examiner requires Applicants to elect species of gene for claims reciting genes, but apparently continues to indicate that the broader claims, which do not recite specific genes,

will be examined without being limited to specific claims). Applicants understand the Election/Restriction requirement as comprising one restriction requirement and one election of species requirement.

Applicants reserve the right to file a divisional application to claims not rejoined in the present application.

The Commissioner is hereby authorized to charge any fees which may be required at any time during the prosecution of this application without specific authorization, or credit any overpayment, to Deposit Account Number 16-0877.

Respectfully submitted,



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Date: November 9, 2009